OsteoArthritis and Cartilage (2005) **13,** 872–878

doi:10.1016/j.joca.2005.06.010

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

The relationships between bone mineral density in the spine, hip, distal femur and proximal tibia and medial minimum joint space width in the knees of healthy females[1]

K. A. Beattie B.Sc.†*, P. Boulos M.D., F.R.C.P. (C)‡, J. Duryea Ph.D.§, J. O'Neill M.D., F.R.C.P.‖, M. Pui M.D., F.R.C.P. (C)¶, C. L Gordon Ph.D.††, C. E. Webber Ph.D.‡‡ and J. D. Adachi M.D., F.R.C.P. (C)‡

† *Department of Medical Sciences, McMaster University, Hamilton, ON, Canada*
‡ *Department of Medicine, St. Joseph's Healthcare, McMaster University, Hamilton, ON, Canada*
§ *Department of Radiology, Brigham and Women's Hospital, Boston, MA, USA*
‖ *Department of Radiology, St. Joseph's Healthcare, Hamilton, ON, Canada*
¶ *Department of Radiology, McMaster University Medical Centre, Hamilton, ON, Canada*
†† *Department of Radiology, McMaster University, Hamilton, ON, Canada*
‡‡ *Department of Nuclear Medicine, Hamilton Health Sciences, Hamilton, ON, Canada*

Summary

Objective: To investigate the relationships between bone mineral density (BMD) in the hip, spine, distal femur and proximal tibia and minimum joint space width (mJSW) in the knees of healthy women.

Methods: Women 22–68 years old without a history of knee pain, bone or joint disease or injury underwent a single, fixed-flexion knee X-ray. Radiographs were graded according to the Kellgren–Lawrence scale and analyzed for mJSW using a computer algorithm. Dual X-ray absorptiometry scans of the spine, hip, distal femur and proximal tibia were also acquired for each participant. Femur and tibia scans were acquired and analyzed using a modified version of the lumbar spine software.

Results: Forty-five females, mean [standard deviation (SD)] age and body mass index (BMI) of 40.1 (13.9) years and 24.6 (4.5) kg/m^2, respectively, participated. The mean (SD) mJSW was 4.64 (0.68) mm. Linear regression analyses controlling for age and BMI revealed that BMD in the femoral trochanter and the central two regions of the tibia (T2 and T3) was significantly related to mJSW in the knee. A backwards regression analysis performed to determine which region of interest is most significantly related to mJSW revealed that femoral trochanter BMD (β-value = 0.416) is the most significant.

Conclusions: In contrast to the suggestion that BMD is negatively correlated with mJSW in the knees of osteoarthritic individuals, these results suggest that increasing BMD in the femoral trochanter and tibia is significantly associated with increasing mJSW in healthy females. Further investigation of this relationship is warranted.

Key words: Minimum joint space width, Knee, Bone mineral density, Osteoarthritis.

Introduction

There appears to be a direct relationship between bone mineral density (BMD) and the presence and severity of hip and knee osteoarthritis (OA)[1–7]. The incidence of knee OA has been observed to be associated with higher adjusted baseline BMD at the lumbar spine and proximal femur as compared to those without OA (i.e., those with normal radiographs)[3,5,8]. In patients suffering from hip OA, the sites of interest for BMD measurements are those regions such as the proximal femur and lumbar spine which lie in close proximity to the hip joint. Consequently, to explore the relationship between knee OA and BMD it is logical to assess BMD in local areas where the stress is greatest[9]. In fact, evidence from both animal and human studies suggests subchondral bone located in closest proximity to the joint may play a significant role in the initiation and/or progression of OA[10–16]. The notion of abnormal remodeling of subchondral bone in OA was described in a review by Lajeunesse and Reboul[16] in which the evidence for abnormal osteoblastic metabolism was explored and the role of cytokines, growth factors and prostaglandins in the initiation and/or progression of OA was discussed. It has been suggested that the production of cytokines, growth factors and prostaglandins by osteoblasts in subchondral bone may be involved in initiating cartilage degeneration. By leaking through fissures and channels in the bone to the

[1] *Institution*: McMaster University & St. Joseph's Healthcare, Hamilton, ON, Canada.

Grants/Support: Karen Beattie is a Ph.D. candidate at McMaster University. Her research is funded by a joint grant from the Canadian Arthritis Network (CAN) and Procter & Gamble Pharmaceuticals Canada, Inc.

Dr Pauline Boulos' Research Fellowship is supported by a combined grant from the Arthritis Society/Canadian Institutes of Health Research.

*Address correspondence and reprint requests to: Karen Beattie, Department of Medical Sciences, McMaster University, Hamilton, ON, Canada. Tel: 1-905-527-9100; Fax: 1-905-521-1297; E-mail: karen.beattie@camris.ca

Received 18 June 2004; revision accepted 20 June 2005.

bone–cartilage interface, these factors have the ability to stimulate cartilage breakdown[16–18]. In addition, an increase in biochemical markers of bone formation and resorption has also been shown to be increased in patients with OA, possibly a reflection of abnormal remodeling and low bone mineralization[13,16,19–22]. Although pre-clinical and clinical studies have shown that an increase in structural BMD is associated with OA, in actual fact it is suggested that the material density of the tissue is decreased[23]. The apparent increase in BMD appears because the total volume of trabecular bone increases as a result of trabecular thickening, and the number of trabeculae may also increase reflected by the radiographic presence of subchondral sclerosis. However, what has been seen to actually occur is a decrease in mineralization of subchondral bone due to the increased rate of bone remodeling which does not allow the bone to fully mineralize, thereby reducing its stiffness[24,25].

A study of the effect of axial deformity on tibial bone mass showed BMD to be higher in the medial rather than the lateral compartment of the knee in those with varus deformity[9]. Because varus deformities are often seen in cases of knee OA affecting the medial compartment, this might suggest that subchondral BMD will be higher in areas where OA is present, although this has not yet been studied. The absence of normal or ''reference'' ranges of BMD in peripheral regions of the body makes it difficult to classify measured BMD values as low, normal or increased. In addition, there is no standardized method of evaluating BMD in the proximal tibia or, for that matter, in the distal femur. Different studies have employed various techniques of measurement making data comparisons between studies difficult.

Not only is there a gap in our knowledge of peripheral bone density as it relates to OA, there is little data available on the relationship of BMD to joint space width in the knee. This data may aid in our understanding of the relationship between subchondral bone activity and cartilage degeneration in OA. Currently, the primary structural outcome measure used in clinical trials of knee OA is the quantification of minimum joint space width (mJSW). This variable has been shown to be a surrogate measure of cartilage degradation in the joint[26]. mJSW is measured from plain film X-rays either with or without fluoroscopic guidance. The non-fluoroscopic techniques have been found to be reproducible and are more cost-efficient and more adaptable to multi-center use than those that are fluoroscopic[26,27]. Films are then analyzed either manually or with the use of an automated computer algorithm. The automated technique has been shown to be more accurate and reproducible than manual methods[28,29]. Longitudinal analyses of mJSW in patients can indicate that cartilage is breaking down and mJSW narrowing is occurring suggesting that, in the most severe cases, there will be eventual bone on bone contact. Recently, Bruyere *et al.*[30] identified a significant correlation between subchondral BMD in the proximal tibia and future joint space narrowing in the medial tibiofemoral compartment of the knee in patients with OA.

Knowing the current state of our understanding of subchondral bone and OA, the issue of the state of subchondral bone density in healthy individuals arises. With the lack of ''normal'' reference values of subchondral BMD available the relative term ''high'' bone density lacks significance. In comparing subchondral BMD in healthy individuals with those affected by knee OA, it is possible that we will learn more about the disease pathophysiology. In addition, the question of whether or not peripheral bone density correlates with other radiographic evidence of OA including joint space width measurements remains to be seen[12,21]. The purpose of this paper is to quantify subchondral bone density in the distal femur and proximal tibia regions and to investigate the relations between BMD in the hip, spine, distal femur and proximal tibia and mJSW in the knees of healthy women.

Materials and methods

Female volunteers between 20 and 69 years of age were recruited to participate via advertisements posted in a local medical building and via word of mouth, provided they were free of knee pain, had never sustained a knee injury nor been previously diagnosed with a bone or joint disease (i.e., rheumatoid arthritis, osteoporosis, etc.). Participants consented to have a single knee X-ray and dual X-ray absorptiometry (DXA) scans of their corresponding distal femur and proximal tibia as well as the proximal femur and lumbar spine. All scans were performed during a single clinic visit. Demographic data were collected through a questionnaire which was administered to participants prior to scanning. The results from this study are a subanalysis of a larger study which includes healthy males, patients with knee OA and the addition of magnetic resonance imaging of the knee. The study was approved by the Research Ethics Board at St. Joseph's Healthcare in Hamilton, Ontario.

X-RAY

Each participant underwent a single X-ray of the non-dominant knee. Radiographs were taken in the fixed-flexion position such that the patient stood on both feet with great toes touching the vertical table and feet externally rotated by approximately 10°[26,31]. While holding the sides of the vertical table for balance, subjects were asked to bend their knees slightly such that their patellas and thighs were pressed tightly against the table. In doing so, the position of the femur and tibia is fixed. The posteroanterior X-ray beam was directed parallel to the tibial plateau (10° caudal beam alignment). A foot map was traced for each individual to reproduce patient positioning for subsequent knee X-rays.

X-ray images were graded by two independent radiologists according to the Kellgren–Lawrence (K–L) scoring system. In the case where the radiologists did not agree on the K–L grade assigned to an X-ray, the X-ray was viewed by both radiologists simultaneously and a consensus grade was assigned. The purpose of the grading was to ensure that knees were, indeed, free of OA. Only those images which scored a 0 or a 1 on the K–L scale were included in the results reported in this paper. Those with a score of ≥ 2 were considered to have knee OA and thus were excluded.

X-rays were digitized using a Sierra plus™ digitizer (Vidar Systems Corporation, Herndon, VA, USA) at an isotropic pitch of 84.7 μm and a 12 bit grey scale resolution. The digitized images were further analyzed for mJSW in the medial compartment of the knee using an automated computer algorithm, details of which have been described previously[26,29].

BONE MINERAL DENSITY

Dual photon absorptiometry scans of the lumbar spine and non-dominant hip were acquired using a Hologic Delphi™ DXA scanner (Hologic Inc., Bedford, MA, USA). For the distal femur and proximal tibia scans, subjects lay in a supine position with the leg of interest held in place by

a polycarbonate positioning device. Using this device, knee flexion of 5° was achieved by placing a curved polycarbonate insert behind the knee while the lower extremity was placed in a foot plate and internally rotated by approximately 10°. This position has been found to optimize both the knee joint space and the separation of the fibula from the tibia[32]. Prior to starting the distal femur scan, the laser crosshair was positioned 5 cm distal to the inferior border of the patella and proceeded 24 cm proximally (Fig. 1). Before starting the proximal tibia scan, the laser crosshair was positioned 23 cm distal to the superior border of the patella and proceeded proximally 24 cm. The femur or tibia was positioned such that the shaft appeared vertically straight and that the epiphysis was centered on the imaging screen. Distal femur and proximal tibia scans were acquired using the lumbar spine scanning software associated with the Delphi machine. The distal femur and proximal tibia DXA scans were analyzed using the protocol as described elsewhere[32]. Each of the femur and tibia are divided into four distinct regions, F1–F4 and T1–T4, respectively, where F1 and T1 are the most proximal and F4 and T4 are most distal (Figs. 2 and 3).

Data collected from the X-ray and DXA scans included mJSW in the medial compartment of the knee and BMD in the lumbar spine, hip, total distal femur, total proximal tibia and subchondral regions of the femur and tibia, respectively. Correlations between central and peripheral BMD values were assessed by Pearson correlation coefficients. Multiple regression analyses were performed to evaluate the value of age, body mass index (BMI) and BMD as they relate to medial mJSW. Results were considered statistically significant at the 5% level ($P < 0.05$). All analyses were carried out using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL).

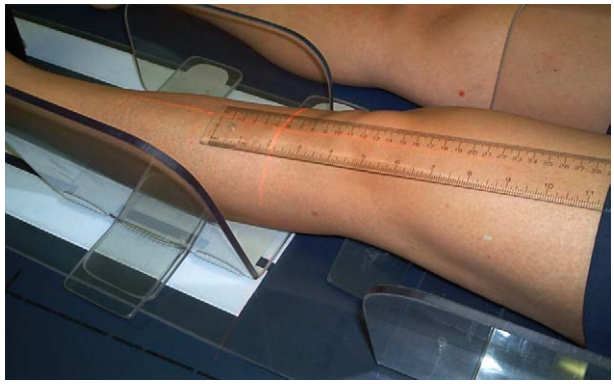

Fig. 1. Positioning of laser crosshair for scanning of distal femur.

Results

Of the 48 women who were eligible to participate in this study, data from three were excluded as both radiologists assessed their X-rays were as being a K–L grade 2. Thus, despite the fact that these women are asymptomatic, radiographic evidence suggested the presence of early radiographic degenerative changes in their knees reflective of mild knee OA. The remaining 45 females ranged in age from 22 to 68 years with a mean [standard deviation (SD)] of 40.1 (13.9) years. The numbers of individuals in each assigned age group are as follows: 14 were between 20 and 29 years of age, 8 were 30–39 years, 10 were 40–49 years, 8 were 50–59 years and 5 were 60–69 years. The group's mean (SD) height, weight and BMI were 1.66 (0.07) m, 67.8 (14.4) kg and 24.6 (4.5) kg/m^2, respectively. K–L grading of X-rays revealed 32 with a K–L grade 0 and 13 with a K–L grade 1. One radiologist (MP) scored all 45 radiographs twice using the K–L score. The intra-rater reliability revealed a statistically significant Pearson's correlation coefficient ($P < 0.05$) of 0.698. The other radiologist reviewed 41 of the radiographs twice, again yielding a statistically significant correlation coefficient of 0.571. The inter-rater reliabilities were also calculated with correlations at both the first and second ratings producing statistically significant coefficients of 0.521 and 0.549, respectively. It is important to note that the distinction between a grade of 0 and a grade of 1 on the K–L scale is not objectively well defined with a 0 being "no narrowing of joint space or osteophytic lipping" and 1 being "the presence of doubtful narrowing of joint space and possible osteophytic lipping". However, it should be recognized that both grades 0 and 1 are considered to be "healthy", and thus there was complete agreement both within and between readers as to whether there was evidence of OA or not. The overall mean (SD) mJSW in the medial compartment of the knee was 4.64 (0.68) mm with a range between 3.37 mm and 6.52 mm. BMDs in the lumbar spine, hip, distal femur and proximal tibia regions are as shown in Table I.

Initially, analyses were also conducted to investigate whether BMI and age were significantly related to mJSW in this population under study. Using a backwards regression model, neither BMI nor age was significantly related to mJSW ($P > 0.05$). Linear regression analyses were also

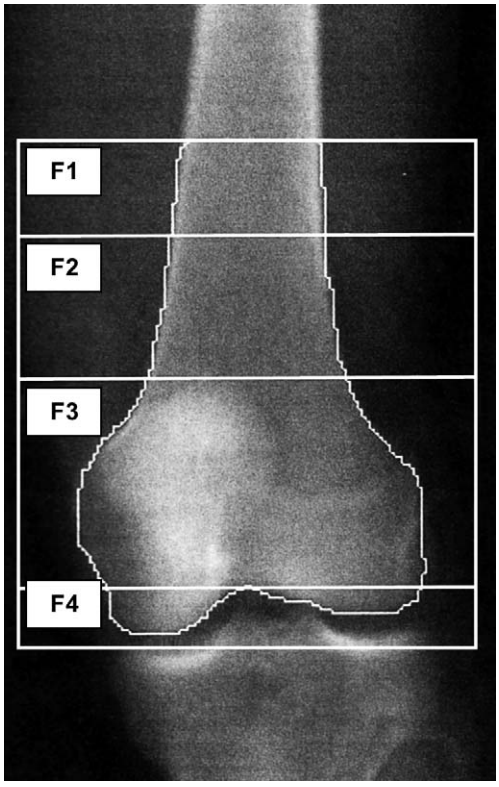

Fig. 2. Analysis of distal femur scan. BMD is calculated in each of four regions of the bone.

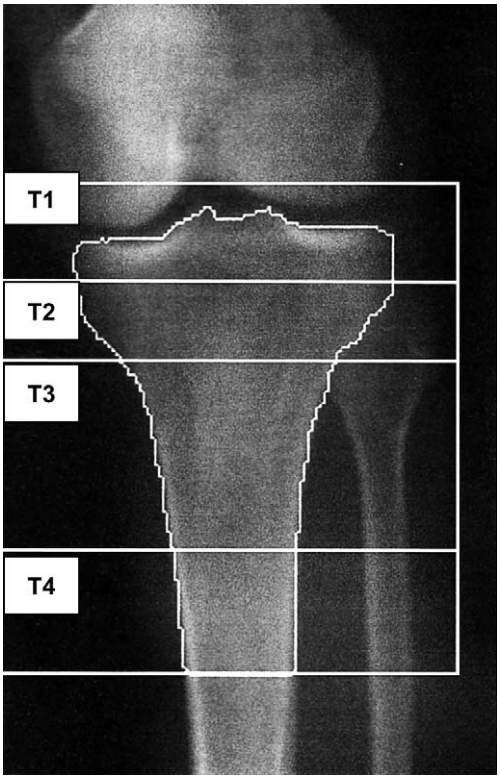

Fig. 3. Analysis of proximal tibia scan. BMD is calculated in each of four regions of the bone.

performed to investigate the value of BMD in various regions of the body in relating to mJSW in the knee. Controlling for age and BMI, bone densities in the regions of the lumbar spine, femoral neck, femoral trochanter and total hip were independently inserted into a backwards regression analysis to determine if any of these variables significantly related to mJSW. Separately, age and height were not found to significantly relate to mJSW ($P > 0.05$) and thus they were not included in the regression model. Results are shown in Table II where β represents the slope of the regression line. It is evident that only BMD in the trochanter of the femur significantly correlated with mJSW in the knee. The same backwards regression analyses also controlling for age and BMI were performed independently for the four areas of interest in each of the distal femur and proximal tibia scans. The total distal femur and total proximal tibia values (representing the mean BMD of the four regions) were also tested in backwards regression analyses. Only those regions of interest which were significantly related to mJSW in the medial compartment of the knee are presented in Table II. Neither the femoral regions of interest nor the total femoral BMD were found to correlate significantly with mJSW. In addition, neither the subchondral region of the tibia (T1) nor the most distal region of the tibia (T4) significantly related to mJSW. However, both the central two regions of the tibia, T2 and T3, were found to be significant, as well as the total tibial BMD.

Following these analyses, the four regions of interest found to be significantly related to mJSW were inserted into a backwards regression analysis to determine which region was the most significant. However, tests for collinearity revealed inflation factors ≥ 10 for the three regions of the tibia under examination suggesting that BMD in these three

Table I
Values of BMD in the lumbar spine, hip and regions of the distal femur and proximal tibia

	Mean (g/cm^2)	SD (g/cm^2)	Minimum (g/cm^2)	Maximum (g/cm^2)
Lumbar spine	1.034	0.100	0.800	1.211
Femoral neck	0.832	0.101	0.644	1.027
Femoral trochanter	0.721	0.100	0.522	0.909
Total hip	0.959	0.115	0.557	1.148
F1 Femur	0.907	0.116	0.690	1.141
F2 Femur	0.809	0.100	0.609	0.984
F3 Femur	1.092	0.133	0.818	1.483
F4 Femur	0.940	0.112	0.617	1.131
Total femur	0.989	0.109	0.765	1.273
T1 Tibia	0.886	0.118	0.608	1.146
T2 Tibia	0.796	0.119	0.512	1.048
T3 Tibia	0.953	0.114	0.686	1.142
T4 Tibia	1.150	0.126	0.902	1.402
Total tibia	0.931	0.110	0.657	1.150

regions is closely correlated with one another and may impact the estimate of the regression coefficient if used as independent variables. Thus, only one region of the tibia and the femoral trochanter were applied to the backwards regression analysis. Results from this analysis yielded a significant ($P = 0.005$) β-value of 0.416 (slope of line) for BMD at the femoral trochanter and a non-significant β-value for tibial BMD. A scatterplot of this analysis is seen in Fig. 4.

Discussion

The use of DXA to evaluate BMD has long been accepted as the gold standard for its application as a diagnostic tool and a technique for evaluating longitudinal changes in osteoporosis. The usefulness of the evaluation of bone density in OA, more specifically in the periarticular regions, has not been extensively explored. Previous studies, however, have found DXA scans to produce images of sufficient quality to allow the precise evaluation of subchondral bone density[33–35]. Researchers have employed various techniques and scanning protocols to assess subchondral BMD both in clinical and cadaveric research settings[9,12,30]. Increasingly, research has shown that subchondral bone may play a very important role in the

Table II
The relationship between BMD in the spine, hip and proximal tibia and mJSW in the medial compartment of the knee

	β-value	*P*-value
Lumbar spine	0.245	0.105
Femoral neck	0.228	0.131
Femoral trochanter	0.383	0.009*
Total hip	0.282	0.061
T1 Tibia	0.282	0.064
T2 Tibia	0.362	0.016*
T3 Tibia	0.324	0.032*
T4 Tibia	0.288	0.058
Total tibia	0.352	0.019*

The * denotes statistical significance at $P < 0.05$ level.

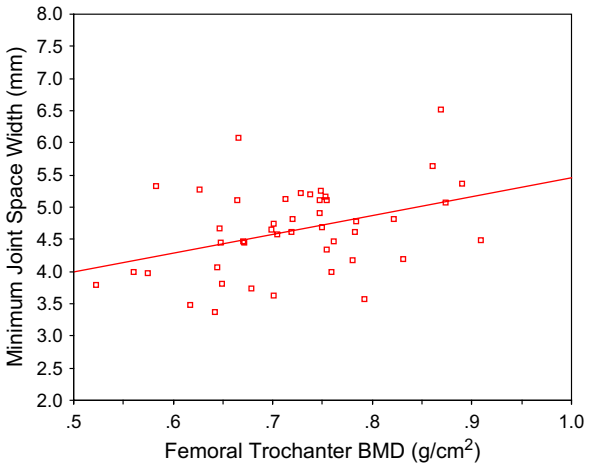

Fig. 4. Linear regression line fit to scatterplot of femoral trochanter BMD vs mJSW.

pathophysiology of OA. Thus, measuring bone density in the subchondral region and its relation to joint space width in healthy people may contribute to our knowledge of the pathogenesis of OA.

The majority of research investigating the relationship between BMD and features of OA, both in the hip and knee, suggests that a high lumbar spine or proximal femur BMD is associated with the presence of sclerotic bone, osteophytes and joint space narrowing. In addition, studies have also suggested that BMD around the area of the affected joint is negatively correlated with joint space width in osteoarthritic patients meaning that a higher BMD is associated with a smaller joint space width[15,30]. The presence of a high bone density in the subchondral region surrounding an osteoarthritic joint has been explored by a number of research groups and possible explanations for these findings have been discussed in recent publications[16,24,36]. It has been suggested that although subchondral bone appears to be denser in osteoarthritic individuals compared to healthy individuals, in actual fact the bone is less mineralized suggesting that the higher BMD values observed are due to reasons other than an increase in bone mineralization. This has recently been shown in a study of osteoarthritic hips by Mkukuma *et al.*[23] where there was less mineral content in subchondral bone from an osteoarthritic hip than in healthy and osteoporotic individuals. Explanations for the apparent increases in bone density were discussed in papers by Burr[24] and Lajeunesse and Reboul[16]. To summarize, bone density appears to increase because of an increase in subchondral trabecular bone volume and perhaps an increase in trabecular thickening. However, it has been demonstrated that subchondral trabecular and cortical bone are actually less mineralized in those with OA compared to those without it[37–39] suggesting that BMD in the subchondral region does not increase as has been observed, but actually decreases. Another potential reason for the actual reduction in BMD may be the abnormal collagen content in subchondral bone[16]. Together with the higher ratio of $\alpha 1$ to $\alpha 2$ chains of type-1 collagen in the subchondral bone of osteoarthritic individuals as compared to non-osteoarthritic individuals, the over-hydroxylation of lysine residues in collagen fibrils and the decrease in cross-links observed in OA bone may help to explain the actual decrease in bone mineralization[16]. An advance in the tidemark and an associated increase in the thickness of the very stiff calcified cartilage, a tissue which may be more mineralized than bone, with a simultaneous decrease in hyaline cartilage thickness have also been observed in OA. These observations may also aid in explaining the increase in subchondral BMD that has been seen in studies[24]. Again, a decrease in articular cartilage thickness shown by a decrease in mJSW is thought to be associated with an apparent increase in BMD[24].

Until now, however, the relationship between subchondral bone density and mJSW has not been investigated in healthy individuals. The findings of this study suggest that BMD in the region of the femoral trochanter is significantly related to mJSW in the knees of healthy females. Using a linear regression analysis, this particular region was the only one of the lumbar spine and hip regions to have significant relationship (β-value = 0.383). However, it is evident that despite the lack of statistical significance of these various regions, all linear regression analyses yielded positive β-values suggesting that increasing BMD is associated with increasing mJSW measurements in healthy women. Likewise, the middle regions of interest of the tibia and the mean BMD of the four regions of interest in the tibia were also significantly related to mJSW in the medial compartment of the knee. Data from the Framingham study published in 2000 suggest that women with a high femoral neck BMD or a gain in BMD may be associated with an increased risk of developing knee OA and a decreased risk of knee OA progression[40]. This study might suggest that following these ''healthy'' women with BMD values in the higher range of normal longitudinally may lead to a finding of an increased incidence of knee OA compared to a female population with the lower BMD values.

It should be noted, however, although these results were adjusted for significant confounding variables as previously stated, they were not adjusted for bone size. Bone size is related both to bone density and mJSW although our analyses did not permit this parameter to be accurately measured. In addition, bone area and bone mineral content were not entered into the statistical analyses independently but rather only taken into account in the form of BMD. It is possible that entering these variables into a regression analyses could potentially reveal additional information about the relationship between subchondral bone and mJSW. These variables will be taken into account in future studies.

In assembling all this information, apparent high bone density values in the spine, hip or subchondral regions are associated with features of OA such as joint space narrowing. However, as discussed above, higher BMD values in the subchondral regions of osteoarthritic individuals may, in fact, be falsely elevated due to the increase in bone volume and bone mass and may not reflect the actual reduction in material bone density. Thus, patients with OA may actually have lower than normal BMD levels and this may actually be associated with a small mJSW reflective of the joint disease. Higher BMD values may actually reflect increasing disease severity and may then indicate decreasing joint space width values and joint space narrowing over time. In healthy women, however, results from this study suggest that increasing BMD at the femoral trochanter and proximal tibia appears to be indicative of larger mJSW values. It is also possible that the relationship between BMD and mJSW in healthy individuals observed here may exist as a result of normal growth, meaning that those healthy individuals with more ''healthy'' or ''true'' mineralization in the bone may also have thicker cartilage resulting in larger joint space widths, while those with less

mineralized bone may have thinner cartilage. Currently, we are in the process of collecting data investigating absolute values of areal bone density and mJSW and the relationship between these variables in the osteoarthritic population.

Unfortunately, the lack of a standardized technique implemented for the measurement of subchondral BMD makes the comparison of results between studies difficult. In addition, research conducted in osteoarthritic individuals has reported minimal data on the actual values of BMD yielded in studies making it difficult to compare measurements between OA patients and healthy volunteers. In knowing these values it might be possible to suggest a threshold subchondral BMD value above which mJSW begins to decrease. Without reference ranges of "normal" values of subchondral BMD, the meanings of "high" and "low" BMD are relative terms that lack meaning and relevance. Thus, there is a need for the establishment of these normal ranges in healthy men and women in order to further investigate the relationship with mJSW in both healthy and osteoarthritic individuals.

With an increasing amount of research being dedicated to the area of subchondral bone in OA, it is important to conduct these studies in healthy individuals in order that "normal" values and relationships be evaluated. In addition, based on what is known about subchondral bone and OA pathophysiology, research in the development of newly emerging disease modifying osteoarthritic drugs might also implement subchondral BMD measurements as a potential outcome measures in clinical trials. However, the need to establish a standardized scanning protocol and analytical technique is of primary importance in order to compare results across trials and to establish relationships among variables.

References

1. Belmonte-Serrano MA, Bloch DA, Lane NE, Michel BE, Fries JF. The relationship between spinal and peripheral osteoarthritis and bone density measurements. J Rheumatol 1993;20(6):1005–13.
2. Stewart A, Black AJ. Bone mineral density in osteoarthritis. Curr Opin Rheumatol 2000;12(5):464–7.
3. Sowers M, Lachance L, Jamadar D, Hochberg MC, Hollis B, Crutchfield M, *et al*. The associations of bone mineral density and bone turnover markers with osteoarthritis of the hand and knee in pre- and perimenopausal women. Arthritis Rheum 1999;42(3): 483–9.
4. Stewart A, Black A, Robins SP, Reid DM. Bone density and bone turnover in patients with osteoarthritis and osteoporosis. J Rheumatol 1999;26(3):622–6.
5. Hart DJ, Cronin C, Daniels M, Worthy T, Doyle DV, Spector TD. The relationship of bone density and fracture to incident and progressive radiographic osteoarthritis of the knee: the Chingford Study. Arthritis Rheum 2002;46(1):92–9.
6. Lethbridge-Cejku M, Tobin JD, Scott WW Jr, Reichle R, Roy TA, Plato CC, *et al*. Axial and hip bone mineral density and radiographic changes of osteoarthritis of the knee: data from the Baltimore Longitudinal Study of Aging. J Rheumatol 1996;23(11):1943–7.
7. Dequeker J, Aerssens J, Luyten FP. Osteoarthritis and osteoporosis: clinical and research evidence of inverse relationship. Aging Clin Exp Res 2003;15(5): 426–39.
8. Hochberg MC, Lethbridge-Cejku M, Tobin JD. Bone mineral density and osteoarthritis: data from the Baltimore Longitudinal Study of Aging. Osteoarthritis Cartilage 2004;12(Suppl A):S45–8.
9. Hulet C, Sabatier JP, Souquet D, Locker B, Marcelli C, Vielpeau C. Distribution of bone mineral density at the proximal tibia in knee osteoarthritis. Calcif Tissue Int 2002;71(4):315–22.
10. Bobinac D, Spanjol J, Zoricic S, Maric I. Changes in articular cartilage and subchondral bone histomorphometry in osteoarthritic knee joints in humans. Bone 2003;32(3):284–90.
11. Matsui H, Shimizu M, Tsuji H. Cartilage and subchondral bone interaction in osteoarthrosis of human knee joint: a histological and histomorphometric study. Microsc Res Tech 1997;37(4):333–42.
12. Yamada K, Healey R, Amiel D, Lotz M, Coutts R. Subchondral bone of the human knee joint in aging and osteoarthritis. Osteoarthritis Cartilage 2002;10(5):360–9.
13. Burr DB, Schaffler MB. The involvement of subchondral mineralized tissues in osteoarthrosis: quantitative microscopic evidence. Microsc Res Tech 1997;37(4): 343–57.
14. Burr DB. The importance of subchondral bone in osteoarthrosis. Curr Opin Rheumatol 1998;10(3): 256–62.
15. Goker B, Sumner DR, Hurwitz DE, Block JA. Bone mineral density varies as a function of the rate of joint space narrowing in the hip. J Rheumatol 2000;27(3): 735–8.
16. Lajeunesse D, Reboul P. Subchondral bone in osteoarthritis: a biologic link with articular cartilage leading to abnormal remodeling. Curr Opin Rheumatol 2003; 15(5):628–33.
17. Imhof H, Breitenseher M, Kainberger F, Rand T, Trattnig S. Importance of subchondral bone to articular cartilage in health and disease. Top Magn Reson Imaging 1999;10(3):180–92.
18. Sokoloff L. Microcracks in the calcified layer of articular cartilage. Arch Pathol Lab Med 1993; 117(2):191–5.
19. Lajeunesse D. The role of bone in the treatment of osteoarthritis. Osteoarthritis Cartilage 2004;12(Suppl A): S34–8.
20. Bailey AJ, Mansell JP, Sims TJ, Banse X. Biochemical and mechanical properties of subchondral bone in osteoarthritis. Biorheology 2004;41(3–4):349–58.
21. Bailey AJ, Mansell JP. Do subchondral bone changes exacerbate or precede articular cartilage destruction in osteoarthritis of the elderly? Gerontology 1997;43(5): 296–304.
22. Mansell JP, Bailey AJ. Abnormal cancellous bone collagen metabolism in osteoarthritis. J Clin Invest 1998;101(8):1596–603.
23. Mkukuma LD, Imrie CT, Skakle JM, Hukins DW, Aspden RM. Thermal stability and structure of cancellous bone mineral from the femoral head of patients with osteoarthritis or osteoporosis. Ann Rheum Dis 2005;64(2):222–5.
24. Burr DB. The importance of subchondral bone in the progression of osteoarthritis. J Rheumatol Suppl 2004; 70:77–80.
25. Coats AM, Zioupos P, Aspden RM. Material properties of subchondral bone from patients with osteoporosis or osteoarthritis by microindentation testing and electron probe microanalysis. Calcif Tissue Int 2003; 73(1):66–71.

26. Peterfy C, Li J, Zaim S, Duryea J, Lynch J, Miaux Y, *et al*. Comparison of fixed-flexion positioning with fluoroscopic semi-flexed positioning for quantifying radiographic joint-space width in the knee: test–retest reproducibility. Skeletal Radiol 2003;32(3):128–32.
27. Boulos P, Beattie K, Jurriaans E, Duryea J, Adachi JD, Gordon C. Minimum medial joint space width reproducibility using an automated technique. J Rheumatol 2002;29:1566.
28. Buckland-Wright JC, Macfarlane DG, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. Ann Rheum Dis 1995;54(11): 872–80.
29. Duryea J, Li J, Peterfy CG, Gordon C, Genant HK. Trainable rule-based algorithm for the measurement of joint space width in digital radiographic images of the knee. Med Phys 2000;27(3):580–91.
30. Bruyere O, Dardenne C, Lejeune E, Zegels B, Pahaut A, Richy F, *et al*. Subchondral tibial bone mineral density predicts future joint space narrowing at the medial femoro-tibial compartment in patients with knee osteoarthritis. Bone 2003;32(5):541–5.
31. Peterfy CG. Imaging of the disease process. Curr Opin Rheumatol 2002;14(5):590–6.
32. Moreno J. Protocol for Using Dual Photon Absorptiometry Software to Measure Bone Mineral Density of the Distal Femur and Proximal Tibia. Hamilton, Ontario, Canada: McMaster University 2001.
33. Madsen OR, Schaadt O, Bliddal H, Egsmose C, Sylvest J. Bone mineral distribution of the proximal tibia in gonarthrosis assessed *in vivo* by photon absorption. Osteoarthritis Cartilage 1994;2(2): 141–7.
34. Murphy E, Bresnihan B, FitzGerald O. Validated measurement of periarticular bone mineral density at the knee joint by dual energy x ray absorptiometry. Ann Rheum Dis 2001;60(1):8–13.
35. Pastoureau PC, Chomel AC, Bonnet J. Evidence of early subchondral bone changes in the meniscectomized guinea pig. A densitometric study using dual-energy X-ray absorptiometry subregional analysis. Osteoarthritis Cartilage 1999;7(5):466–73.
36. Burr DB. Anatomy and physiology of the mineralized tissues: role in the pathogenesis of osteoarthrosis. Osteoarthritis Cartilage 2004;12(Suppl A):S20–30.
37. Li B, Marshall D, Roe M, Aspden RM. The electron microscope appearance of the subchondral bone plate in the human femoral head in osteoarthritis and osteoporosis. J Anat 1999;195(Pt 1):101–10.
38. Li B, Aspden RM. Composition and mechanical properties of cancellous bone from the femoral head of patients with osteoporosis or osteoarthritis. J Bone Miner Res 1997;12(4):641–51.
39. Grynpas MD, Alpert B, Katz I, Lieberman I, Pritzker KP. Subchondral bone in osteoarthritis. Calcif Tissue Int 1991;49(1):20–6.
40. Zhang Y, Hannan MT, Chaisson CE, McAlindon TE, Evans SR, Aliabadi P, *et al*. Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham Study. J Rheumatol 2000;27(4):1032–7.